REMARKS

Claims 1, 4-5, 8, and 13-18 are pending. Claims 2-3, 6-7, and 9-12 were previously cancelled. Claims 1, 4, and 5 are currently amended. Claims 8 and 17-18 are cancelled without prejudice. Applicants reserve the right to pursue the cancelled matter in a continuation application. Applicants submit that no new matter has been added. Claim amendments are supported within the claims themselves.

Withdrawal of Rejections

Applicant thanks the Examiner for withdrawal of the rejections for lack of enablement, lack of written description, and obviousness for the reasons recited in the Office Action.

Claim Objections

The Examiner has objected to claims 4, 5, 17, and 18 for containing informalities. Applicant thanks the Examiner for the careful reading of the claims. The claims have been amended per the suggestion of the Examiner. Withdrawal of the objections is respectfully requested.

Claim Rejections

Rejection of Claims 1-2, 4-5, and 8-16 under 35 U.S.C. §112, second paragraph

The Office Action has rejected claims 4, 5, and 17 under 35 U.S.C. §112, second paragraph. The Office Action alleges that the claims fail to particularly point out the subject matter to be claimed. Applicant respectfully disagrees. However, the claims have been amended to recite the language from claim 1 which is not rejected for being indefinite making the claims definite.

Applicant accordingly requests that the rejection be reconsidered and withdrawn.

Rejection of Claims under 35 U.S.C. §103(a)

Claims 1, 4-5, 8, and 14-18 are rejected under 35 U.S.C. §103(a) over Perlak et al. (PNAS, 1991) in view of Joshi (Nuc. Acids Res., 1987) and further in view of Dancis Dancis (PNAS , 1991).

Applicant respectfully disagrees.

The Office Action asserts that Perlak teaches a method of making a transgenic plant and seeds derived therefrom by introducing and expressing a modified heterologous coding sequence *crylA*(b) gene of *Bacillus thuringiensis* in transgenic tobacco and tomato plants. The transgenic plants exhibited improved insect resistance. The modification did not alter the amino acid sequence of the heterologous CryIA(b) protein. The Office Action further asserts that Joshi teaches plant gene sequences having GT-rich sequences resembling animal GT-rich sequences found downstream of polyA sites. The Office Action also asserts that Joshi teaches that deletion analysis in the 3' untranslated region of plant mRNA transcripts reveals a region 30 to 80 bases downstream AATAAA comprises GT rich motifs that are also required for correct and efficient polyadenylation of plant mRNA transcripts. The Office Action then relies on Dancis to teach a nucleic acid sequence which is heterologous to a plant, and encoding yeast ferric-chelate reductase FRE1 (a protein involved in absorption of iron, a plant nutrient).

To reach a proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant"s disclosure is often difficult to avoid due to the very nature of the

examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. (See MPEP 2142)

To arrive at the instantly claimed invention, one of skill in the art would have needed to know that yeast FRE1 would not be transcribed as a full length transcript in a plant cell. One of skill in the art would not have expected this as it was known that yeast genes could be transcribed and translated in plants without modification. This is distinct from transcription and translation of bacterial genes as bacteria are evolutionarily quite distinct from plants. It was only upon determining that there was a problem that the inventors were able to solve the problem. In the absence of some teaching or suggestion that would have motivated one "when the invention was unknown and just before it was made" to combine the references as suggested in the Office Action, the rejection cannot stand.

Perlak teaches making a transgenic plant by providing a prokaryotic gene to a plant for the purpose of providing insect resistance. The instantly claimed invention includes providing a eukaryotic gene, specifically a *Saccharomyces cerevisiae* ferric-chelate reductase FRE1, for providing a nutrient transporter. Perlak describes that difficulties in introducing bacterially derived genes from *Bacillus* into plants were overcome by modifying the coding sequence without modifying the translated amino acid sequence.

The present invention describes the expression of a yeast gene in a plant. Evolutionarily the yeast from which the gene is obtained very close to plant being introduced into the plant. The same is not true for bacterial genes.

As described in the specification of the instant application, (paragraph 68 as published, third paragraph on page 10 of the application as filed) a yeast gene, *e.g.* yeast invertase gene, can be used for the synthesis of full length invertase mRNA plants. Therefore, before the filing the instant application, it had been known in the art

that yeast genes are generally less divergent from plants than bacterial genes. Moreover, codon usage in yeast and plants were known to be similar. The gene when expressed natively in yeast does not have a premature termination or addition of a poly-A tail on other than full-length transcripts. The same would be expected in plants.

Until the inventors determined that the FRE1 yeast gene was improperly processed in plants, there could be no motivation to combine the references to arrive at the instant invention as no problem had been identified. Only upon determination that expression of yeast FRE1 in plants resulted in premature termination of transcription, there would be no motivation to make the instantly claimed invention. Moreover, even upon detection of the premature termination of transcription, the reason for the premature termination could not be identified.

The present inventors had considered that reason that full length mRNA could not be synthesized in the FRE1-transformed tobacco. The inventors hypothesized that the truncation was due to "a part of mRNA [that] was spliced as intron" (paragraph 65 as published, page 10, paragraph 3). However, further analysis by RT-PCR by the inventors demonstrated for the first time the poly(A) addition to the mRNA had occurred. It is truly remarkable that despite being yeast derived gene, poly(A) addition is observed within plants, and synthesis of full length mRNA is completely inhibited. This could not be predicted based on difficulties of expression of bacterial proteins in plants.

Joshi describes that deletion analysis in the 3'-untranslated region of plant mRNA transcripts reveals a region 30 to 80 bases downstream AATAAA comprises "GT rich motifs" that are also required for "polyadenylation signal of plant mRNA transcripts".

As described above, in order to find out why synthesis of full length mRNA was inhibited in the yeast derived gene FRE1, the present inventors performed analysis by RT-PCR as described in detail in Example 3 and Figure 3. They determined that poly(A) addition was observed at a position around 541-680. Although the adjacent sequence of the poly(A) site was AAUAA like sequence ("AATAAA sequence") and several "AATAAA sequence" were observed at 5'-site of FRE1 where was further

upstream from the position around 541-680, the poly(A) addition was not observed in these positions. These results demonstrate that the presence of an AT rich sequence is insufficient to promote polyadenylation and other sequences are required.

From comparison and intensive study of these base sequences around "AATAAA sequence" of both upstream and adjacent of the poly(A) site, the results as described in Example 3 and shown below were reached.

"It may be a GU-rich sequence located in the upstream of the poly(A) signal to determine addition of poly(A) in plant. Namely, if GU-rich sequence exists, addition of poly(A) may be occurred in the plant, and in the position of "PolyA", which is located at the distance of 10-30 bp from the subsequently appeared AAUAAA like sequence, mRNA is splitted, then the poly(A) may be added by an action of poly(A) polymerase."

In conclusion, the fact that GU-rich sequence, which has no relation to addition of poly(A) in yeast, determines addition of poly(A) in plant, is a cause for not forming full length mRNA in the transgenic tobacco, to which FRE1 is transformed." (page 11, first – second paragraph, paragraphs 71-72 as published)

On the basis of this finding, a putative sequence of yeast FRE1 having "GT-rich region" is shown in the boxed sequences in Fig. 4. See both Fig.3 and Fig.4. In upstream from the position 541-680 where poly(A) addition was observed intensively, there were 2 "GT-rich region"s at the positions 439-480 and 512-522.

Hence, the present invention describes, no relation to the teachings of Joshi. The results based on RT-PCR analysis demonstrate that the "GT-rich region" located in the upstream of the "AATAAA sequence" is actively involved in determination of addition of poly(A). In contrast, Joshi merely discloses GT-motifs in 3'-region are involved in addition of poly(A) in plants in plant derived genes, not GT-rich sequences in heterologous genes. Further, Joshi provides no teachings regarding the positional relation to "AATAAA sequence" in the heterologous gene.

It is highly unlikely that in a yeast derived gene, in spite of presence of "AATAAA sequence" and GT-rich sequence in a base sequence thereof, would be identified as a poly(A) site by plants such that the transcription of full length mRNA is completely inhibited.

In view of the absence of the technical knowledge provided by the instant application, it is unlikely that one of ordinary skill in the art would be motivated to modify a yeast derived gene similarly to *Bacillus* derived gene based on the teaches by Perlak. Further, even if one of ordinary skill in the art would have been motivated to modify "AATAAA sequence", it's highly unlikely that one would be motivated to further modify also GT-rich sequence when a sufficient expression has been obtained by modification of "AATAAA sequence" alone in the yeast derived gene, or even in Bacillus derived gene.

Applicant notes that simply because references can be combined does not provide motivation to combine the references. In the absence of some teaching or suggestion that there would be an advantage to modify the specifically claimed sequence of a yeast gene for expression in plants based on the teachings of modification of a bacterial gene, the rejection cannot stand.

Furthermore, neither Perlak nor Joshi teach specifically how and to what extent to modify AATAAA sequence or GT-rich sequence. Additionally they provide no teachings regarding how to modify specific yeast derived FRE1 gene.

In contrast, the instant invention describes that base sequences of the specific yeast derived FRE1 gene were studied in detail, and the need to modify AATAAA sequence to a sequence not "comprising AATAAA sequence as well as sequences substituted any one base to other base of said sequence, i.e. NATAAA, ANTAAA, AANAAA, AATNAA, AATANA or AATAAN", and for encoding identical amino acid, and to modify GT-rich sequence for "not comprising 8 or more consecutive sequences of only G or T and for encoding identical amino acid." By the above finding the present invention was been accomplished.

The specific sequence of FRE1 provided by Dancis further provides no motivation to modify the sequence for expression in plants.

The Office Action has rejected claim 13 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Perlak et al. (PNAS, 88:3324-3328, April 1991) in view of Joshi (Nucleic Acids Research, 15:9627-9640, 1987), and Dancis et al. (PNAS, 89:3869-3873, Published May 1992) as applied to claims 1, 4-5, 8 and 14-17 above, and further in view of D'Halluin et al. (Plant Cell, 4:1495-1505, December 1992).

Applicant respectfully disagrees.

The rejection of claim 13 relies on the combination of Perlak, Joshi, and Dancis. The combination of the references cannot be proper or make the instantly claimed invention obvious for at least the reasons set forth above. D'Halluin does not cure these deficiencies.

There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the cited references to make the claimed invention, nor is there a reasonable expectation of success. Accordingly, reconsideration and withdrawal of the rejection are requested.

Further, Applicant notes that claims similar in scope to the instantly pending claims were allowed in Japan (Japanese Patent No. 3920453) after a similar obviousness/ inventive step rejection by the Japanese Examiner. A copy of the claims are provided in Appendix A for reference.

Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

It is believed that there is no fee due with this response. However, if a fee is due, the Commissioner is hereby authorized to charge Deposit Account 04-1105 referencing Docket No. 55022DIV(71526) any fee due with this response or any other paper filed by this firm in relation to this application. Credit of any overpayment to the account is respectfully requested.

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Respectfully submitted,

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